UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,066	09/20/2001	Hazire Oya Alpar	41577/263691	4735

,23370 7590 01/31/2008

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
ATLANTA, GA 30309

EXAMINER	
HINES, JANA A	
ART UNIT	**PAPER NUMBER**
1645	

MAIL DATE	DELIVERY MODE
01/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/937,066	ALPAR ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6,11-17,20-22,37 and 40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6,11-17,20-22,37 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered.

Amendment Entry

2. The amendment filed October 31, 2007 has been entered. Claims 1, 16, 17 and 37 have been amended. Claims 2, 4, 7-10, 18-19, 23-36 and 38-39 have been cancelled. Claims 1, 3, 5-6, 11-17, 20-22, 37 and 40-43 are under consideration in this office action.

Withdrawal of Objections

3. The objection of claim 37 under 37 CFR 1.75(c) has been withdrawn in view of applicants' amendment.

Response to Arguments

4. Applicant's arguments filed October 31, 2007 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3, 6, 11-17, 37 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eyles (1998. Vaccine. Vol.16(7):698-707) in view of Kotze et al., (J. of Pharm. Sci. Vol.88(2):253-257, published online 12/5/1998).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan with a degree of quaternization that is at least 20% and N-carboxymethyl chitosan or a salt thereof. Claim 3 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethylchitosan with a degree of quaternization that is at least 40%. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres,

microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. Claim 13 is drawn to the first material capable of forming particles is a polymeric material which has a molecular weight of 100kDa or more. Claim 14 is drawn to the first material capable of forming particles comprises poly-(L-lactide). Claim 15 is drawn to the ratio of the first material capable of forming particles to the polycationic carbohydrate is from 99:1 to 9:1 w/w. Claim 16 is drawn to the biologically active agent is capable of generating a protective immune response against tetanus, anthrax, diphtheria, or *Yersinia pestis*. Claim 17 is drawn to the biologically active agent comprising a combination of the V antigen of *Y. pestis* or an immunologically active fragment thereof, and the F1 antigen of *Y. pestis* or an immunologically active fragment thereof. Claim 37 is drawn to the biologically active agent being able to produce an immune response against tetanus, anthrax, diphtheria, or *Yersinia pestis* in an animal to which it is administered. Claim 40 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethyl chitosan with a degree of quaternization that is at least 60%. Claim 41 is drawn to a composition comprising a biologically active agent and a polycationic carbohydrate. Claim 42 is drawn to the polycationic carbohydrate comprising a water-soluble alkylated chitosan and a positively charged molecule. Claim 43 is drawn to the positively charged molecule comprising a cationic peptide, cationic polyamino acid or a quarternary ammonium compound.

Eyles et al., teach a pharmaceutical composition comprising poly-(L-lactide) microspheres co-encapsulated with *Yersinia pestis* V and F1 subunits that confer protection from pneumonic plague in mice (page 699, col.2). Eyles et al., teach that the

F1 antigen confers resistance to phagocytosis and both F1 and V antigens are protective, although there is an additive effect in the combination (page 698, col.2). It is noted that the F1 peptide subunit is a glycoprotein. The commercially purchased poly-(L-lactide) has a molecular weight of 100 kDa and was used in a modified double emulsion solvent evaporation method (page 699, col.2). It is noted that Eyles et al., teach the use of such microparticles and/or spheres and the associated chemical compounds and the claimed ratios. No more than routine skill is required to change the concentration or ratio of well known compositions and such changes do not impart patentability to the composition.

Eyles et al., teach effective vaccination requires affecting or utilizing musocal surfaces as portals of entry (page 698-699, col.2-1). Furthermore Eyles et al., teach that mucosal vaccination advantageously offers some degree of the induction of systemic immunity in concert with local responses due to translocation of antigenic material (page 699, col.1). Eyles teach that simple mucosal applications are ineffective because of enzymatic or chemical destruction, combined with poor absorption; therefore encapsulation of antigenic material within microparticulate polymeric carriers such as poly-DL-lactide protect the vaccines from degradation and enhance mucosal and systemic absorption (page 699, col.1). However Eyles et al., do not teach pharmaceutical compositions comprising trimethyl chitosan chloride that is at least 20% quarternized.

Kotze et al., teach pharmaceutical compositions comprising N-trimethyl chitosan chloride (TMC) that is 61.2% quarternized (abstract). Kotze et al., teach that TMC with

higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of compounds (page 253, col.2). Kotze et al., teach TMC is able to significantly increase the transport of hydrophilic compounds and peptide drugs (page 253, col.2). Kotze et al., teach that TMC interacts with components of glycoproteins (page 256, col.2).

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the pharmaceutical composition comprising a biologically active agent as taught by Eyles et al., wherein the modification incorporates the use of trimethyl chitosan chloride that is at least 20% quarternized as taught by Kotze et al., in order to increase absorption across mucosal surfaces. One of ordinary skill in the art would be motivated to modify the microparticle compositions as taught by Eyles et al., because Eyles et al., teach that effective compositions capable of generating a protective immune response require utilizing musocal surfaces as portals of entry; thus one of ordinary skill in the art would have a reasonable expectation of success in providing microparticle compositions with further significantly increased mucosal absorption which is beneficial to the recipient without the disadvantage of enzymatic or chemical destruction, combined with poor absorption. No more than routine would have been required to modify the composition of Eyles et al., by incorporating the trimethyl chitosan chloride that is at least 20% quarternized, because Kotze et al., teach higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of peptide compounds and/or glycoproteins, while Eyles teach et al., that the F1 antigen is both a peptide drug and a glycoprotein. Furthermore, the

limitations drawn to the ratios of particles to the polycationic carbohydrate, trimethyl chitosan are viewed as merely optimizing the experimental parameters and not imparting patentability; thus no more than routine skill would have been required to change the concentration in the well known compositions as taught by Eyles et al., in view of Kotze et al.

Response to Arguments

6. The rejection of claims 1, 3, 6, 11-17, 37 and 40-43 under 35 U.S.C. 103(a) as being unpatentable over Eyles (1998. Vaccine. Vol.16(7):698-707) in view of Kotze et al., (J. of Pharm. Sci. Vol.88(2):253-257, published online 12/5/1998) is maintained.

Applicants' argue that Eyles fails to teach or suggest a composition containing a polycationic carbohydrate and, because Eyles is silent with respect to polycationic carbohydrates, the Eyles reference fails to teach a polycationic carbohydrate possessing an increased degree of quaternization. However, the composition of claim 1 only comprising a biologically active agent and a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan with a degree of quaternization that is at least 20% and N-carboxymethyl chitosan or a salt thereof; which Eyles in view of Kotze et al., teach.

Applicants' argue that Eyles does not discuss the need for or use of a polycationic carbohydrate. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually

where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants' argue that Eyles teaches that the antigens must be encapsulated to be effective. However, there is no limitations within the claims that prevent the antigens from being encapsulated. The claims recite open language which allows for additional reagents, thus there are no restrictions within the claims that prevent the encapsulated antigens from meeting the limitations of the biologically active agents.

Furthermore, contrary to applicants arguments, the Office's position is that if the prior art structure is capable of performing the intended use, then it meets the claim. In this case the prior art is capable of performing the intended function. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Therefore "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). As such applicants' claim of surprising and unexpected results surrounding the composition is not persuasive.

Applicants' assert that Kotze et al., teach that chitosan are ineffective, and thereby undesirable. However Kotze et al., teach pharmaceutical compositions comprising N-trimethyl chitosan chloride that is 61.2% quarternized wherein higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of compounds. While applicants assert that the TMC with 12.3%

quaternization was ineffective, thus one of skill in the art would avoid using the TMC of Kotze et al. However, it is the examiner's position that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). The invention was directed to an epoxy impregnated fiber-reinforced printed circuit material. The applied prior art reference taught a printed circuit material similar to that of the claims but impregnated with polyester-imide resin instead of epoxy. The reference, however, disclosed that epoxy was known for this use, but that epoxy impregnated circuit boards have "relatively acceptable dimensional stability" and "some degree of flexibility," but are inferior to circuit boards impregnated with polyester-imide resins. The court upheld the rejection concluding that applicant's argument that the reference teaches away from using epoxy was insufficient to overcome the rejection since "Gurley asserted no discovery beyond what was known in the art." 27 F.3d at 554, 31 USPQ2d at 1132. Therefore contrary to applicants' argument, the prior art does not teach away from the instant claims. Kotze et al., clearly teach the benefits of higher quarternized compounds. Kotze et al., teach higher degrees of quarternization are more effective as absorption enhancers. Kotze et al., teach increases in paracellular transport of compounds. Therefore applicants' arguments are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies i.e., that the composition that allows for the delivery of hydrophobic compounds) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would be motivated to modify the microparticle compositions as taught by Eyles et al., because Eyles et al., teach that effective compositions that generate a protective immune response; therefore one of ordinary skill in the art would have a reasonable expectation of success in providing microparticle compositions with further significantly increased mucosal absorption which is beneficial to the recipient without the disadvantage of enzymatic or chemical destruction, combined with poor absorption. Moreover, no more than routine would have been required to modify the composition of Eyles et al., by incorporating the trimethyl chitosan chloride that is at least 20% quarternized, because Kotze et al., teach higher degrees of quarternization are more

effective as absorption enhancers and increase the paracellular transport of peptide compounds and/or glycoproteins, while Eyles teach et al., that the F1 antigen is both a peptide drug and a glycoprotein.

Claim Rejections - 35 USC § 103

7. Claims 1, 3, 6, 11-12, 16, 37 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (WO 97/20576 published June, 1997) in view of Kotze et al., (J. of Pharm. Sci. Vol.88(2):23-257, published online 12/5/1998).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan with a degree of quaternization that is at least 20% and N-carboxymethyl chitosan or a salt thereof. Claim 3 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethylchitosan with a degree of quaternization that is at least 40%. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. Claim 16 is drawn to the biologically active agent is capable of generating a protective immune response against tetanus, anthrax, diphtheria, or *Yersinia pestis*. Claim 37 is drawn to the biologically active agent being able to produce an immune response against tetanus, anthrax, diphtheria, or *Yersinia pestis* in an animal to which it is

administered. Claim 40 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethyl chitosan with a degree of quaternization that is at least 60%. Claim 41 is drawn to a composition comprising a biologically active agent and a polycationic carbohydrate. Claim 42 is drawn to the polycationic carbohydrate comprising a water-soluble alkylated chitosan and a positively charged molecule. Claim 43 is drawn to the positively charged molecule comprising a cationic peptide, cationic polyamino acid or a quarternary ammonium compound.

Illum teaches vaccine compositions comprising one or more biologically active agents capable of generating a protective immune response in an animal, an effective adjuvant and the polycationic carbohydrate, chitosan (page 1, lines 1-6). Illum teaches suitable antigens include tetanus toxoid and diphtheria toxoid (pages 4-5, lines 23-1). Illum teaches the pharmaceutical compositions are formulated in the form of microspheres (page 6, lines 22-24). Illum teaches that chitosans are known as mucosal absorption enhancers and upon administration, chitosan enhances the immune response of antigens and provides an enhanced effect upon the host (page 3, lines 1-6). However Illum does not teach pharmaceutical compositions comprising trimethyl chitosan chloride that is at least 20% quarternized.

Kotze et al., teach pharmaceutical compositions comprising N-trimethyl chitosan chloride (TMC) that is 61.2% quarternized (abstract). Kotze et al., teach that TMC with higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of compounds (page 253, col.2). Kotze et al., teach

TMC is able to significantly increase the transport of hydrophilic compounds (page 253, col.2).

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the pharmaceutical composition comprising a biologically active agent as taught by Illum, wherein the modification incorporates the use of trimethyl chitosan chloride that is at least 20% quarternized as taught by Kotze et al., in order to increase absorption across mucosal surfaces. One of ordinary skill in the art would be motivated to modify the compositions as taught by Illum, because Illum teach the need for chitosans, which are well known mucosal absorption enhancers that also enhance the immune response of antigens; thereby providing a reasonable expectation of success. Thus one of ordinary skill in the art would have a reasonable expectation of success in providing compositions having higher degrees of quarternization, since Kotze et al., teach that a 61.2% quartenized trimethyl chitosan are more effective as absorption enhancers. No more than routine would have been required to modify the composition of Illum et al., to instead incorporate the trimethyl chitosan chloride that is at least 20% quarternized, because Kotze et al., teach that higher degrees of quarternization increase the paracellular transport of compounds. Finally it would have been advantageous to incorporate trimethyl chitosan that is at least 20% quarternized in the pharmaceutical composition, in order to achieve an enhanced effect upon the host.

Response to Arguments

8. The rejection of claims 1, 3, 6, 11-12, 16, 37 and 40-43 under 35 U.S.C. 103(a) as being unpatentable over Illum (WO 97/20576 published June, 1997) in view of Kotze et al., (J. of Pharm. Sci. Vol.88(2):23-257, published online 12/5/1998) is maintained.

Applicant argues that the Illum reference teaches away from the claimed invention because Illum discloses the use of chitosan glutamate as an adjuvant. However, it is the examiner's position that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). The invention was directed to an epoxy impregnated fiber-reinforced printed circuit material. The applied prior art reference taught a printed circuit material similar to that of the claims but impregnated with polyester-imide resin instead of epoxy. The reference, however, disclosed that epoxy was known for this use, but that epoxy impregnated circuit boards have "relatively acceptable dimensional stability" and "some degree of flexibility," but are inferior to circuit boards impregnated with polyester-imide resins. The court upheld the rejection concluding that applicant's argument that the reference teaches away from using epoxy was insufficient to overcome the rejection since "Gurley asserted no discovery beyond what was known in the art." 27 F.3d at 554, 31 USPQ2d at 1132. Therefore contrary to applicants' argument, the prior art does not teach away from the instant claims because

it would have been prima facie obvious at the time of applicants' invention to modify the pharmaceutical composition comprising a biologically active agent as taught by Illum, wherein the modification incorporates the use of trimethyl chitosan chloride that is at least 20% quarternized as taught by Kotze et al., in order to increase absorption across mucosal surfaces.

In response to applicant's arguments against the Illum reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants' argue that Kotze et al., fail to teach a composition capable of generating a protective immune response. The fact that the art discloses that the composition may be used as for a different use does not distinguish the instant claims over the art. A known or obvious composition does not become patentable simply because it has been described as having a different use, especially when that use is not claimed. Therefore contrary to applicants' argument that they are claiming the protective immune response; the prior art does not teach away from the instant claims, since the prior art teaches compositions comprises exactly the same components as the instant claims. Thus the additional or other uses are irrelevant. Applicants' assert that the instant composition has the feature of having the antigen and adjuvant distributed throughout the composition. However in response to applicant's argument, a recitation of the intended use of the claimed invention must result in a structural difference

between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Moreover, the claim does not include any additional components which the prior art does not have. Therefore applicants' argument is not persuasive.

Claim Rejections - 35 USC § 103

9. Claims 1, 3, 5-6, 11-12, 20-22, 37 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan et al., (WO 94/20070 published September 1994) in view of Kotze et al., (J. of Pharm. Sci. vol.88(2):23-257, published online 12/5/1998).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan with a degree of quaternization that is at least 20% and N-carboxymethyl chitosan or a salt thereof. Claim 3 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethylchitosan with a degree of quaternization that is at least 40%. The pharmaceutical of claim 5 is drawn to the pharmaceutical composition further comprising a cationic polyamino acid. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. The pharmaceutical of claim 20 is drawn to the

pharmaceutical composition further comprising a cationic polyamino acid and/or a cationic pluronic. Claim 21 is drawn to the pharmaceutical composition further comprising a cationic pluronic. Claim 22 is drawn to the composition comprising particles of the cationic pluronic which are surface modified with the polycationic carbohydrate. Claim 37 is drawn to a biologically active agent which is able to produce an immune response in an animal to which it is administered. Claim 40 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethyl chitosan with a degree of quaternization that is at least 60%. Claim 41 is drawn to a composition comprising a biologically active agent and a polycationic carbohydrate. Claim 42 is drawn to the polycationic carbohydrate comprising a water-soluble alkylated chitosan and a positively charged molecule. Claim 43 is drawn to the positively charged molecule comprising a cationic peptide, cationic polyamino acid or a quarternary ammonium compound.

Duncan et al., teach compositions comprising: i) biologically active agents, such as immunogens or antigens at pages 4-5 para.1, ii) an adjuvant chemical having adjuvant properties wherein the adjuvants include Pluronic™ block copolymers also known as cationic pluronics and polyamino acids such as polyarnithine at pages 9-10, para. 1; and iii) an acceptable carrier such as a mucoadhesive at page 6, para.1. Duncan et al., further teach that an enhancement in the immune response is observed when the adjuvant is combined with the immunogen and muchoadhesive (pages 10-11, para.2). The antigens are more immunogenic when they are incorporated into the

polymeric microparticles, nanoparticles or liposomes (page 2, para.4). However Duncan et al., do not teach pharmaceutical compositions comprising trimethyl chitosan chloride that is at least 20% quarternized.

Kotze et al., teach mucoadhesive pharmaceutical compositions comprising N-trimethyl chitosan chloride (TMC) that is 61.2% quarternized (abstract). Kotze et al., teach that TMC with higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of compounds (page 253, col.2). Kotze et al., teach TMC is able to significantly increase the transport of hydrophilic compounds (page 253, col.2).

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known trimethyl chitosan compositon as taught by Kotze et al., and modify the compositions to include the biologically active antigen and adjuvant agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Duncan et al., in order to enhance the muchoadhesive properties. One of ordinary skill in the art would have a reasonable expectation of success by modifying the pharmaceutical compositions as taught by Duncan et a., because Duncan et al., teach the need for muchoadhesive which provide further enhancement in the immune response. Thus one of ordinary skill in the art would have a reasonable expectation of success in providing compositions having higher degrees of quarternization, since Kotze et al., teach that trimethyl chitosan chloride that is at least 60% quarternized is more effective as absorption enhancers. No more than routine would have been required to modify the composition

of Duncan et al., to instead incorporate the trimethyl chitosan chloride that is at least 20% quarternized, because Kotze et al., teach that higher degrees of quarternization increase the paracellular transport of compounds, into the pharmaceutical composition of Duncan which already comprises a muchoadhesive combined with biological active antigens and cationic pluronic in microparticle formation to achieve enhanced mucosal absorption. Finally it would have been advantageous to incorporate trimethyl chitosan that is at least 20% quarternized in the pharmaceutical composition, in order to achieve an enhanced effect upon the host.

Response to Arguments

10. The rejection of claims 1, 3, 5-6, 11-12, 20-22, 37 and 40-43 under 35 U.S.C. 103(a) as being unpatentable over Duncan et al., (WO 94/20070 published September 1994) in view of Kotze et al., (J. of Pharm. Sci. vol.88(2):23-257, published online 12/5/1998).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, no more than routine would have been required to modify the composition of Duncan et al., to instead

incorporate the trimethyl chitosan chloride that is at least 20% quarternized, because Kotze et al., teach that higher degrees of quarternization increase the paracellular transport of compounds, into the pharmaceutical composition of Duncan which already comprises a muchoadhesive combined with biological active antigens and cationic pluronic in microparticle formation to achieve enhanced mucosal absorption. Therefore, it would have been advantageous to incorporate trimethyl chitosan that is at least 20% quarternized in the pharmaceutical composition, in order to achieve an enhanced effect upon the host.

Conclusion

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
January 14, 2008

MARK NAVARRO
PRIMARY EXAMINER